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Heterogeneously Catalyzing C-C Coupling Reactions with Precious Metal Nanoparticles

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Abstract

C-C coupling reactions are ubiquitous in synthetic chemistry, joining together fragments of larger molecules within overall synthetic schemes. Many obvious operational advantages would result from catalyzing such processes heterogeneously, however there has been much controversy over whether metal nanoparticles (typically Pd) can be used in this role, or if catalysis in such cases occurs instead on metal ions leached into solution. In this mini-review selected examples of attempts to distinguish the homo- or hetero-geneity of such reactions, using Pd and Au nanoparticles, are highlighted. In particular, several interesting recent results are explored that demonstrate such metal nanoparticle catalyzed reactions can occur in a heterogeneous mode.

Keywords: C-C coupling, heterogeneous, Heck, Suzuki, Sonogashira, mechanistic studies

INTRODUCTION

Metal-catalyzed coupling reactions that result in the formation of new C-C bonds are of paramount importance in synthetic organic chemistry. This fact was recognised by the award of the 2010 Nobel Prize for Chemistry to Heck, Negishi and Suzuki.¹ Their reactions, along with other similar C-C couplings such as Stille and Sonogashira, offer an extremely convenient route to join large fragments of molecules in a controlled manner – vital for designing convergent overall synthetic schemes. In addition to organic synthesis (an arena in which such reactions

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have become indispensable since the first homogeneous organometallic reagents appeared about 40 years ago)² they have also begun to unlock new strategic approaches for the preparation of materials for use in optical and electronics applications.³ For example, they have been used in the production of functional stilbenes and bibenzyls for use in liquid crystals⁴ or the preparation of conjugated oligomers which can be used in light emitting devices.⁵

In the production of fine chemicals and pharmaceuticals, the application of heterogeneous catalysts is especially attractive because of the considerable advantages offered by being able to work in a continuous flow mode, also eliminating the need for subsequent difficult steps to separate catalyst and products. Additionally, supported catalysts are increasingly adopted in the research laboratory, for example in microfluidic devices, for the automated synthesis of chemical libraries.⁶

Heterogeneously catalyzing C-C coupling reactions, conventionally catalyzed by organometallic reagents, would be very advantageous and, as highlighted in a recent tutorial review,⁷ many reports now exist of nanoparticle catalyzed analogues of these reactions. However, mechanistic concerns remain and are the focus of the present mini-review. These are seldom directly investigated concerning whether catalysis takes place heterogeneously on the surface of metal nanoparticles, or at single metal atoms leached into solution. Even when attempts have been made to clarify this point, evidence has been presented in favour of both mechanisms. Accordingly, the answer may very well depend on the reaction and conditions used. The answer to the question of whether a heterogeneous reaction is actually possible is obviously key to any practical application. To be effective, the catalyst must not be leached away as either clusters or atoms, so as to preserve the lifetime of the catalyst and to prevent the often toxic leached metal species contaminating the product. Promisingly, two very different systems have recently been reported to proceed overwhelmingly heterogeneously: oxide-supported gold nanoparticle catalyzed Sonogashira coupling at high temperatures (145 °C),^{8, 9} and unsupported palladium

nanoparticle catalyzed Suzuki coupling at low temperatures (60 °C).¹⁰ Here, these systems and other salient examples and evidence are explored concerning the homo- and hetero-geneity of nanoparticle catalyzed C-C coupling reactions. This mechanistic focus is adopted with a view to achieving the goal of gaining understanding which will be technologically useful in developing future heterogeneous catalysts.

CONVENTIONAL C-C COUPLING REACTIONS

While earlier reports of reactions with harsh reagents such as organolithium and Grignard reagents exist,^{11,12} the generally accepted landmark in the development of organometallic C-C coupling reactions was the publication by two independent researchers on the palladium catalyzed coupling of aryl halides with terminal olefins^{2, 13} – the Heck reaction. As illustrated in Figure 1, after this point many C-C coupling reactions were quickly developed, including the Sonogashira,¹⁴ Stille,¹⁵ and Suzuki-Miyaura¹⁶ couplings.

The typical catalysts for such systems are complexes of palladium with various ligands, though often supplied just as Pd(acac)₂ or Pd(PPh₃)₄. The palladium is then oxidized and reduced between Pd⁰ and Pd^{II} during the catalytic cycle.¹⁷⁻¹⁹ An example of such a catalytic cycle is given in Figure 2, shown here for a Heck coupling of an aryl halide and an olefin. The reactions to couple aryl halides to other molecules are similar with the olefin binding step replaced by a transmetallation where appropriate.[‡] Despite the difficulty of separation, purification and re-use of such homogeneous organometallic catalysts and the need to carefully remove any residual palladium from the reaction product, there exist a number of patents based on this technology.²¹

One notable demonstration illustrated in Figure 3 is the use of Sonogashira coupling reactions

[‡] For the case of reaction with an alkyne (Sonogashira coupling), the homogeneous catalyst often contains a copper co-catalyst homogeneous catalyst, believed to facilitate acetylide formation;²⁰ the reaction then proceeds via a similar mechanism, again with a transmetallation step rather than direct insertion of Pd into the olefin.

in the synthesis of 6-[2-(2,5-Dimethoxyphenyl)ethyl]-4-ethylquinazoline, an antimitotic used in cancer treatment.²² Although this example illustrates the use of such technology, it is still a batch process and the separation stages still form a considerable component of the cost. (Here, the product is separated from Pd by an unusual approach involving crystallization of the product while Pd is held in solution by a binding additive.)

HETEROGENEOUSLY CATALYZED C-C COUPLING

The many advantages of seeking to use truly heterogeneous catalysts have already been discussed. Generally two common approaches exist to achieving this goal. One starts from a homogeneous complex and functionalizes it so that it can be anchored to either an inorganic support or a polymer matrix in order to heterogenize it. However, such heterogenization is complicated by two factors: the immobilization process often appears to decrease catalytic effectiveness and the degradation of such systems by the irreversible leaching of the active metal centre is almost inevitable.²³ Such leaching occurs because, although the complex may be covalently or ionically tethered, the metal centre is typically only held within the complex by co-ordinating ligands.²³ For palladium catalyzed C-C coupling reactions a number of examples of this approach do exist, although it is unclear to what extent the above limitations still apply.²⁴

The other approach is to use a more conventional supported catalyst typical of those used in the petrochemical and bulk chemical industries and consisting of metal nanoparticles on an oxide support. While such catalysts inherently lack the high specificity of a homogeneous catalyst owing to the presence of a variety of active sites rather than a single active metal centre, they offer the considerable payback of achieving the many operational advantages of a truly heterogeneous catalyst as described above; the metal being relatively robustly bound to the matrix. For C-C coupling reactions the use of such metal nanoparticle catalysts is particularly promising. For

these reactions it has been observed that many of the complex ligand-based monometallic[§] complexes are really precursors to the actual catalyst^{25, 26} and that in some way Pd(0) clusters are involved.²⁷⁻³⁰ Equally it has been claimed their role may still be as reservoirs for monometallic species which form, catalyze the reaction then reabsorb into the cluster.³¹

Many reports of nanoparticle catalyzed C-C coupling reactions do already exist, however a key mechanistic issue concerning the identity of the active species is often overlooked and rarely directly addressed.³² Is it the metal nanoparticles or monometallic species leached into solution that catalyse the reaction? Indeed, in the demonstration of polymer based monoliths containing Pd nanoparticles to catalyse the Heck reaction in a flow system unacceptably high levels of palladium could be detected in the initial product; these were captured by a metal scavenger resin at the reactor exit.³³ For small scale applications this is a technically feasible solution but does not address whether the reaction really occurs on the nanoparticles or that the nanoparticles serve merely as source of monometallic Pd. If the latter is in fact the case then all the problems of separation and recovery outlined earlier potentially remain for the heterogeneous catalysis of such reactions.

Even when directly sought, unambiguous evidence as to the homo- or heterogeneity of a reaction often remains elusive, with classic tests giving a body of 'circumstantial evidence' which is heavily dependent on interpretation.²⁰ It has been pointed out by Widegren and Finke³⁴ that many of the classical tests have shortcomings and merely observing or correlating species present doesn't necessarily involve them in the cycle of the active catalyst. Where possible the most reliable results combine such data with kinetic data from a reaction.

Heck Coupling

[§] It should be noted that monometallic is used throughout to refer to entities containing one metal atom which may be co-ordinated by non metallic species, rather than to refer to species containing only one metallic element as is sometimes used.

In the case of Heck reactions, evidence exists pointing to both hetero- and homogeneity of the catalyst. Attempts to correlate rate and the presence of dissolved palladium content do indeed identify a clear correlation.³⁵ Leached anionic palladium species resulting from interactions with organic iodide have been also isolated²⁷ and observed to change oxidation state over the reaction; possibly indicative of their role in the catalytic cycle.³⁶ If all the aryl halide is converted to PhPdI type species before the addition of alkene the reaction also proceeds readily,³⁷ pointing to the fact such species may well offer a pathway by which these reactions can proceed. Filtration^{38, 39} and poisoning^{39, 40} experiments also suggest the reaction proceeds via monometallic species in solution. A more elegant example of the probable homogeneous nature of the reaction was provided by the use of a three phase test, originally applied to hydrogenations,⁴¹ whereby one of the organic substrates is bound to a polymer resin so that only a homogeneous catalyst can diffuse to the reaction site. Grafting the aryl halide to a polymer does not affect the formation of product in the reaction (for Suzuki as well as Heck couplings),⁴² although it has been pointed out that a potential shortcoming of this method is that it cannot distinguish between solution phase clusters small enough to diffuse efficiently and truly monometallic species.³⁴

In a carefully designed recent study by Rothenberg and co-workers a nanoporous alumina membrane (pore size < 11 nm) was used to demonstrate that large Pd clusters (> 11 nm) on one side of the membrane led to catalysis of the reaction on the other.⁴³ However it has already been pointed out¹⁰ that this does not discount the transport of smaller active clusters or the re-formation of nanoparticles from monometallic species which have diffused across the membrane. The formation of such nanoparticles is particularly feasible in view of the long induction period. Indeed, in a subsequent, more ambiguous study using the same technique with a Suzuki coupling TEM analysis identified the appearance of small nanoparticles in the second half of the reactor.⁴⁴

Although many experiments have been described that point to Heck coupling reactions using Pd metal particles as a source of Pd monometallic species, there is also evidence of reactions which appear to be truly heterogeneous in nature. It was found that there is an excellent correlation between surface structure and activity as particle size is varied for a range of polyvinylpyrrolidone (PVP) polymer stabilized Pd colloids (the turnover frequency being constant once normalized to only the edge and corner sites of the particles).⁴⁵ In the same study it was also observed that the initial rate of reaction was substantially less if a Pd salt and the PVP were added separately rather than as pre-formed colloids. This points to a role for the Pd surface sites in the reaction, although not ruling out the surface sites controlling a leaching mechanism that in turn governs a homogeneous catalytic reaction. An interesting study has also been performed using a Pd/PVP functionalized atomic force microscopy probe to spatially initiate a solution phase reaction of aryl halide with a self assembled monolayer of aryl alkenes.⁴⁶ Only reactants contacted with the Pd particles on the probe react providing compelling evidence that mobile leached Pd species do not mediate the reaction in this case. However, it is difficult to ascertain if the contact pressure of the AFM probe promotes a reaction that would not otherwise occur at a significant rate under these conditions.

Suzuki Coupling

Experiments exploring the reaction mechanism of aryl halides with boronic acids catalyzed by palladium nanoparticles appear on balance to point to the catalyst acting truly heterogeneously, although this may be a result of a less extensive number of studies and the particular reaction conditions selected. El-Sayed and co-workers identified the importance of surface sites in the reaction²⁸ and the effect on activity of Ostwald ripening.²⁹ Both these factors point toward the role of the Pd surface in Suzuki coupling reactions. A study using ionic liquids showed again that nanoparticles seemed to play a crucial role in the catalysis, with no evidence for leached Pd

species (although the authors hypothesize the particles could still be acting as a reservoir of such species).³⁰

Adoption of a new approach already used to look at similar homogeneous catalysts,^{47,48} *in situ* X-ray absorption spectroscopy (XAS), has recently allowed the nature of the active species to be interrogated during the reaction. The reaction kinetics were monitored by periodic sampling for offline GC analysis. In one instructive study of this type the authors used an unsupported polyvinylpyrrolidone polymer capped Pd nanoparticle catalyst. The XAS technique probes the co-ordination number of the Pd atoms and hence for the nanoparticles used in the catalyst is very sensitive to changes in particle size or dissolution of monometallic Pd species. A schematic indicating the *in situ* technique setup is provided in Figure 4. It was shown that Suzuki coupling can be performed under mild conditions where Pd leaching cannot be detected during the reaction and the nanoparticles are stable with respect to either sintering or dissolution (corresponding to less than 1/20th of the Pd present being present as solubilized palladium).^{10,49} Furthermore, spiking of the reaction with a Pd salt results in no sudden change in reaction rate, while a mercury poisoning test stops the reaction completely.¹⁰ This all strongly points towards a truly heterogeneous reaction on the surface of the nanoparticles in this instance. Another recent study about the effect of O₂ and H₂O on reduction and aggregation of a Pd(OAc)₂ precursor salt under reaction conditions indicated it was Pd(0) that was the active catalytic species, but a distinction between molecular and colloidal forms could not be drawn.⁵⁰

Sonogashira Coupling

The coupling of aryl halides to an acetylene has also been found to be catalyzed by using Pd and other metal nanoparticles^{9, 20, 51, 52} similar to the reactions above. Mechanistically a PdMgLa mixed oxide has been carefully examined and appears to act as an effective heterogeneous catalyst.⁵³ The catalyst was observed to be recoverable with negligible loss of palladium and recyclable. Nevertheless, the possibilities of re-adsorption of the Pd after reaction or catalysis by

small quantities of leached material were not ruled out. Activity was also lost after hot filtration of the reaction mixture, although without complementary testing of the recovered solid phase with fresh reactants this test has been found to be unreliable; the filtration process can inhibit the reaction by capturing reagents, intermediates or causing a temperature drop.³⁴

Owing to the interest in gold nanoparticle reactions,⁵⁴ and a recent notable example catalyzing this reaction with a gold-ceria nanomaterial,⁹ the gold nanoparticle catalyzed Sonogashira coupling reaction was investigated mechanistically with a series of Au/SiO₂ catalysts and a number of lines of inquiry pointed to the reaction being overwhelming heterogeneous.⁸ As with the Pd catalyzed Heck coupling, a significant particle size effect was found to occur, albeit with different trends and probable origins, pointing to the likely importance of the nanoparticles in the catalytic process. Reaction kinetics also pointed to the gold nanoparticles being the agent responsible for catalysis with extensive deliberate leaching showing the reaction stopped when all the gold was leached into solution. Conversely, starting with a soluble gold complex the reaction showed a long induction period, as illustrated in Figure 5, most likely due to time required for the formation of clusters of gold atoms that were of sufficient size to catalyze the reaction.⁸ The location of the gold was monitored by both ICP-MS of the liquid and XPS of the solid catalyst. The reaction was also observed to occur in vacuum on a Au(111) single crystal surface where no possibility of solution phase chemistry exists.⁵⁵ A further study of the same reaction, coupling iodobenzene to phenylacetylene, also indicated that metallic gold was required for the reaction and a very significant support effect on the selectivity occurs when the nanoparticles were deposited on ceria rather than silica. This again points to a surface mediated catalytic process in which the solid support interacts with the metal nanoparticle.⁵⁶

CONCLUSIONS

For both homogeneous and heterogeneous cases of reactions such as Heck, Suzuki and Sonogashira coupling there has been considerable debate as to the nature of the actual active

species and whether metal nanoparticles or single metal atoms in solution dominate. However a series of recent mechanistic studies for each of these three reactions clearly point to the fact that under quite different conditions they can be made to occur truly heterogeneously. Many operational advantages would result from the heterogeneous catalysis of C-C coupling reactions, which are known to provide a convenient and strategic pathway to join fragments within overall synthetic schemes. Further development and optimization of these systems is undoubtedly necessary, however it is clearly apparent that metal nanoparticle catalyzed C-C coupling reactions are an attractive means for true heterogeneous catalysis of this strategically important class of synthetic reactions.

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FIGURES:

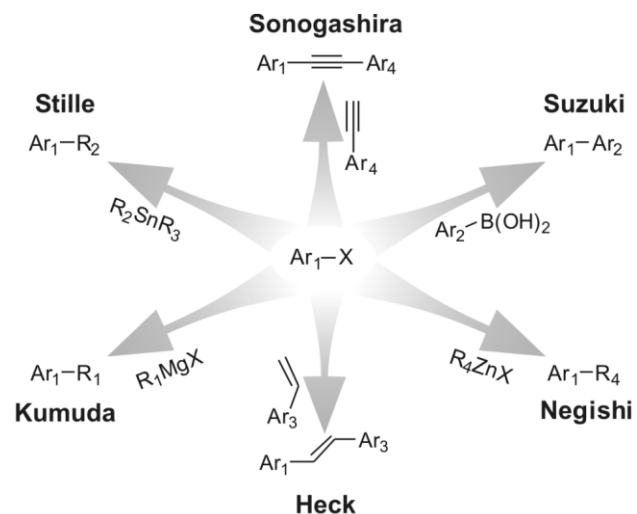


Figure 1: Schematic showing the various key groups of C-C coupling reactions that have been discovered using aryl halides.

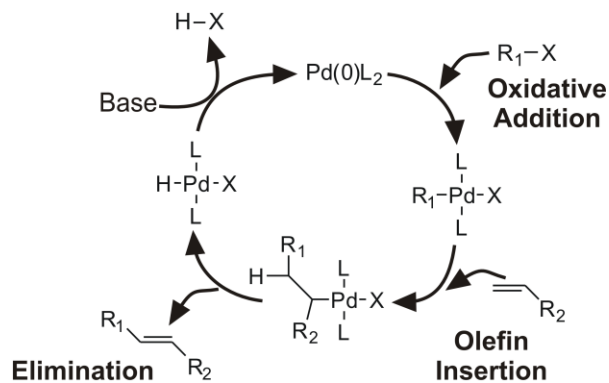


Figure 2: Typical catalytic cycle proposed for the homogeneous Heck reaction between aryl halides and olefins using a ligand based Pd complex.

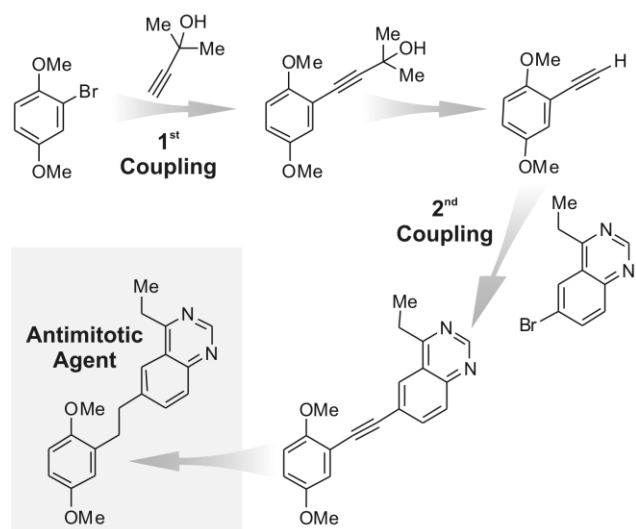


Figure 3: Novartis synthesis of 6-[2-(2,5-Dimethoxyphenyl)ethyl]-4-ethylquinazoline (an antimitotic agent used in cancer treatment) using Sonogashira coupling steps to complete the synthetic scheme.

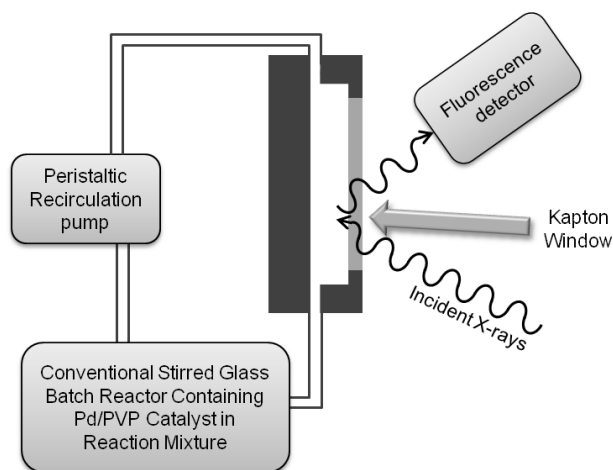


Figure 4: Schematic showing the coupling of a conventional glass batch reactor and a typical *in situ* X-ray cell with an X-ray ‘transparent’ kapton window for EXAFS allowing both reaction kinetics and spectroscopy to be followed for the same reaction (as described in Ref. 10).

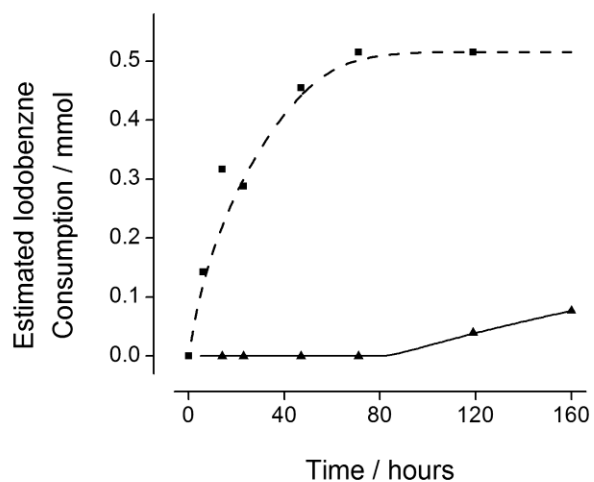


Figure 5: Showing the difference in kinetics (monitored as consumption of reactant) for the reaction of iodobenzene (0.5 mmol) and phenylacetylene (0.5 mmol) [with base K_2CO_3 (0.3 mmol) at 145 °C in Dimethylformamide (7.5 ml)] with a heterogeneous 20 nm particle size Au/SiO₂ catalyst (■) vs. a AuCl(PPh₃) salt (▲), 6 mg of Au being present in each case. The latter does not react until after a long induction period, and then only slowly – likely due to the formation of Au nanoparticles under the conditions of the reaction. (Data taken from Ref. 8.)